Standardization of epidemiologic protocols for surveillance of post-streptococcal sequelae: acute rheumatic fever, rheumatic heart disease and acute post-streptococcal glomerulonephritis

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Introduction

This document was developed by a working group that was convened following meetings supported by the U.S. National Institutes of Health, and the World Health Organization, to discuss the harmonization of protocols for surveillance of group A streptococcal (GAS) diseases. This protocol addresses three post-infectious, immune-mediated sequelae of GAS infection:

- **Acute rheumatic fever**
- **Rheumatic heart disease**
- **Acute post-streptococcal glomerulonephritis**

For the purpose of this document, GAS refers to pathogenic group A, β-hemolytic streptococci and is used synonymously with *Streptococcus pyogenes*. For each disease, the following issues are discussed and recommendations for harmonization are made:

1. **Case Definition**
2. **Aspects of surveillance and expression of disease occurrence**
3. **Core Elements of Case Report Forms**
4. **Standardization of laboratory and echocardiographic testing**

Purpose

The purpose of these guidelines is to allow those performing group A streptococcal surveillance to compare data across studies and geographic regions. They have been designed to be used in epidemiological studies and in vaccine clinical trials. This will allow the results of vaccine efficacy trials to be applied easily to burden data from epidemiological studies conducted at national or subregional level. The use of standard definitions and methods will also simplify the task of developing global burden estimates based on data from individual epidemiological studies.

Acute rheumatic fever

1. Case definition

The definitions used in vaccine clinical trials need to be sufficiently specific to allow accurate estimation of vaccine clinical efficacy. Hence, the definitions described herein may differ from those proposed in an earlier WHO document, which is aimed more at early detection and clinical management.

Acute rheumatic fever (ARF) cases will be categorized as definite or probable. In addition, each episode should be categorized as a primary episode or recurrence. Thus, there are four possible categories for each episode of ARF:

- Definite primary ARF
- Definite recurrent ARF
- Probable primary ARF
- Probable recurrent ARF

A. Recurrences vs primary episodes

Any episode in a patient with no known prior history of ARF or RHD, and who on presentation has no clear evidence of pre-existing RHD, will be considered a primary episode. Any episode in a patient with a known prior history of ARF or RHD, or who on presentation has clear evidence of pre-existing RHD, will be considered a recurrent episode.

To qualify as a recurrence in a patient who has had a recent episode of definite or probable ARF, the symptoms and/or signs of recurrence must begin at least 60 days following the onset of the previous episode AND after the signs of active inflammation in the previous episode have resolved. Specifically, rheumatic arthralgia, arthritis, fever, and pericarditis should have resolved, ESR and/or CRP should be dramatically reduced or normal (in most instances, this means ESR <10 mm/hr and CRP <10 mg/L), and cardiac status should not be continuing to worsen due to active rheumatic inflammation. Persistence of choreiform movements from a prior episode of rheumatic chorea does not exclude the diagnosis of a recurrence, provided the other conditions are met.

B. Definite ARF

A case of acute rheumatic fever will be defined as that fulfilling the 2002-2003 World Health Organization criteria (Table 1). For details of the clinical features of each manifestation, see WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease (2001: Geneva Switzerland). Rheumatic fever and rheumatic heart disease: report of a WHO Expert Consultation, Geneva, 29 October - 1 November 2001. Geneva: World Health Organization, 2004.

Table 1. The 2002-2003 World Health Organization criteria for the diagnosis of rheumatic fever, slightly modified

Primary episode of RF	**Two major or one major and two minor manifestations PLUS evidence of a preceding group A streptococcal infection**	
Recurrent ARF in a patient without established RHD	Two major or one major and two minor manifestations PLUS evidence of a preceding group A streptococcal infection PLUS past history of definite or probable ARF	
Recurrent ARF in a patient with established RHD	Two minor manifestations PLUS evidence of a preceding group A streptococcal infection	
• Rheumatic chorea • Insidious onset rheumatic carditis	Other major manifestations or evidence of group A streptococcal infection not required.	
Major manifestations	Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules	
Minor manifestations	Clinical:	Polyarthralgia Fever
	Laboratory:	Elevated acute phase reactants (C-reactive protein $\geq$30 mg/L, erythrocyte sedimentation rate $\geq$30 mm/hr)* Prolonged PR interval on electrocardiogram†
Evidence of antecedent GAS infection in the last 45 days	Elevated or rising streptococcal antibody titers (ASOT, Anti-DNase B)‡ Positive throat culture or rapid streptococcal antigen test Recent scarlet fever	

Adapted from WHO Expert Consultation on Rheumatic Fever and Rheumatic Heart Disease (2001: Geneva Switzerland). Rheumatic fever and rheumatic heart disease: report of a WHO Expert Consultation, Geneva, 29 October - 1 November 2001. Geneva: World Health Organization, 2004. Please refer to this document (available for free download at http://www.who.int/cardiovascular_diseases/resources/trs923/en/) for information about clinical features of ARF manifestations.

* See "Elevated Acute Phase Reactants", below.

† See "Prolonged P-R interval", below.

‡ See "Elevated or rising streptococcal antibody titers", below.

C. Probable ARF

Cases from a population with known or suspected high rates of ARF and/or RHD not meeting the criteria for definite ARF will be considered probable ARF if they meet **any** of the following criteria, providing that other diagnoses have been carefully excluded:

i. A primary episode with no major manifestations, but with polyarthralgia or monoarthritis, **plus** at least two other (non-joint) minor manifestations **and** evidence of a preceding GAS infection.

ii. A recurrent attack of ARF in a patient **without** established RHD presenting with two minor manifestations **plus** evidence of a preceding group A streptococcal infection.

iii. The presence of at least two minor manifestations **and** evidence of a preceding GAS infection in a person with no clinical manifestations of carditis **and with** no known history of ARF or RHD **but with** echocardiographic evidence of definite or probable RHD (see below*).

* Echocardiographic evidence of definite RHD is **any** of:

a) A mitral regurgitant jet at least 2 cm from the coaptation point of the valve leaflets, seen in two planes and persisting throughout systole **plus** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet.

b) An aortic regurgitant jet at least 1 cm from the coaptation point of the valve leaflets, seen in two planes **plus** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet.

c) Any significant mitral stenosis (defined as flow acceleration across the mitral valve with a mean pressure gradient greater than 4mmHg).

* Echocardiographic evidence of probable RHD is any of:

a) Thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet regardless of the degree of mitral or aortic regurgitation.

b) A mitral regurgitant jet at least 2 cm from the coaptation point of the valve leaflets, seen in two planes and persisting throughout systole **without** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet (in the setting of possible ARF, this may represent acute carditis, before valve leaflets have developed structural abnormalities).

c) An aortic regurgitant jet at least 1 cm from the coaptation point of the valve leaflets, seen in two planes **without** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet

d. Notes about case definition

i. Elevated acute phase reactants

The WHO criteria include only elevated CRP or leucocyte count as acute phase reactants. The Jones Criteria, 1992 update (*JAMA* 1992;268**:**2069-2073) include only elevated CRP or ESR. Australian data found that CRP and ESR were commonly elevated in patients with confirmed ARF, excluding chorea, whereas the leucocyte count usually was not (mean (SD) 12.8 (4.6) x 10^9/L) (*Arch Dis Child* 2001;85:223-7). Further analysis of these data shows that only 25% of ARF patients had a leucocyte count >15 x 10^9/L, and only 7% had a count >20 x 10^9/L. By contrast <4% of patients had both a serum CRP level of less than 30 mg/L and an ESR of less than 30 mm/h. Therefore, we suggest using these values as upper limits of normal for CRP and ESR in the diagnosis of ARF, and not including elevated leucocyte count as an acute phase reactant.

ii. Prolonged P-R interval

The following upper limits of normal for P-R interval should be used: 3-12 yrs 0.16 s, 12-16 yrs 0.18 s, ≥17 yrs 0.20 s. (Adapted from Park MK. Pediatric Cardiology for Practitioners, 2nd edition. Year Book Medical Publishers, Chicago, 1988. p42)

iii. Elevated or rising streptococcal antibody titers.

It is recommended that acute serum be collected at the onset of illness, and that the antibody titer be compared to a convalescent serum collected 2-4 weeks later, to detect a rise in titer.

When paired acute and convalescent titers are not available, an upper limit of normal (ULN) value may be used on a single serum. It is recommended that age-stratified ULN values for serum streptococcal antibody titers be determined in a subset of individuals without a recent streptococcal infection in each population if possible. In many populations, this may not be possible for reasons of logistics, cost, or simply because streptococcal infections are so highly prevalent that it is difficult to identify any children without recent streptococcal infections. In these situations, it is recommended that the ULN levels from three recent studies be used (Table 2).

Table 2. Recommended upper limits of normal for anti-streptolysin O and anti-DNase B titers, in the absence of appropriate local population data.

Age group (yrs)	Upper limit of normal	
	ASO titer	Anti-DNase B titer
2-4	160	240
5-9	240	320-640
10-12	320	480-640
>12	400	200

From: Kaplan EL et al, Pediatrics 1998; 101: 86-8; Gray GC et al. J Clin Epidemiol 1993; 46: 1181-5; and Karmarkar MG et al, Indian J Med Res. 2004;119 Suppl:26-8.

2. Aspects of surveillance and expression of disease occurrence

The primary goal of surveillance for ARF is to determine the age-specific incidence of disease, usually stated as cases per 100,000 person-years. Therefore, the age group and duration of surveillance should be clearly defined.

Secondary expressions of disease burden that may be used are:

- Prevalence of ARF. This has frequently been used in other studies, but has little clinical or epidemiological relevance. ARF is a relatively short-lived illness (in most instances, cases last less than 2 or 3 months even if untreated), so the best measurement of disease burden is incidence, not prevalence. Therefore, the measurement of ARF prevalence is not encouraged.

- Prevalence of a history of ARF or RHD. This has relevance because not all ARF episodes result in chronic RHD, and some people with RHD improve over time, but all people with ARF or RHD require a minimum of five years of secondary prophylaxis (often more) and therefore remain a burden to the health care system. The combined measurement of prevalence of RHD and prevalence of a history of ARF or RHD requiring secondary prophylaxis will give an accurate measurement of the burden of ARF/RHD in a community at a particular time. The details surrounding these calculations are included in Protocol 2.3 – Rheumatic Heart Disease.

a. Age:

The peak incidence of ARF is in children aged 5 to 14 years, inclusively. Therefore, ARF surveillance should always include this age group, and data should always be produced separately for this age group. Investigators may also choose to include other age groups. For example, ARF remains reasonably common in people aged 15-24 years; in this age group, recurrent episodes may feature prominently. ARF becomes steadily less common with increasing age, and is very rare in people aged >40 years. Age group-specific data should be produced in 5 or 10 year age blocks (e.g. 5-14, 15-24, 25-34, etc).

b. Duration of surveillance:

ARF incidence is seasonal in many places, so surveillance should ideally take place over at least 12 months and in multiples of 12 months.

c. Site of ascertainment:

Most cases of ARF will present to hospital, so hospital-based surveillance is mandatory. Investigators should ensure that all hospitals or other clinical establishments (e.g. smaller clinics with inpatient facilities) in the drainage area that could reasonably be expected to manage ARF patients are included. In some populations, ARF cases may occasionally be managed by primary care services or on an outpatient basis. In these regions, investigators may choose to expand surveillance to include these settings. This approach increases the number of sites of surveillance, the cost, and the complexity; in particular, information (especially clinical data recording and performance of tests) is often incomplete in primary care or outpatient settings. The sites of case ascertainment should be clearly stated, and the incidence of cases presenting to hospital should always be reported separately.

d. Identification of potential cases:

Many cases of ARF will not be given an admission diagnosis of ARF. ARF may not even appear on the list of differential diagnoses initially for some cases. Investigators should cast a broad net to ensure that potential ARF cases are not missed. The classic presentation of ARF (fever and arthritis or arthralgia) may be given a wide range of admission diagnoses including septic arthritis, irritable hip, inflammatory arthritis, juvenile chronic arthritis, reactive arthritis, influenza, arboviral arthritis, or osteomyelitis. Similarly chorea may not be specified as rheumatic (or "Sydenham's"), can be confused with other movement disorders (e.g. tics, choreo-athetosis), or the behavioural disturbance may be considered more prominent than the movement disorder initially. Carditis may be confused with other causes of cardiac failure in childhood, particularly congenital heart disease. As well as considering many admission diagnoses as potential cases, investigators should be aware that ARF cases do not always present to the general paediatric or medical services; surgeons (usually orthopaedic), neurologists and cardiologists often look after ARF cases when first admitted to hospital.

Therefore, it is suggested that multiple levels of case ascertainment be established, including routine review of all admissions with an over-inclusive list of admission diagnoses, regular liaison with hospital medical staff in paediatrics and paediatric surgery, and routine review of echocardiography and streptococcal serology results.

e. Investigation of potential cases:

Possible ARF cases need to have a wide range of differential diagnoses excluded, but also need to have clear documentation of how they satisfy the diagnostic criteria. This usually means that the following investigations are needed on all cases (if available):

- Erythrocyte sedimentation rate
- C-reactive protein (quantitative)
- White blood cell count
- Blood cultures if febrile
- Electrocardiogram
- Chest X ray if clinical or echocardiographic evidence of carditis
- Echocardiogram
- Throat swab
- Anti-streptolysin O and anti-DNase B titers
- Depending on clinical features:
    - Repeated blood cultures if possible endocarditis.
    - Joint aspirate (microscopy and culture) for possible septic arthritis
    - Copper, caeruloplasmin, anti-nuclear antibody, drug screen for choreiform movements
    - Serology and autoimmune markers for arboviral*, autoimmune or reactive arthritis

* Note that asymptomatic positive arboviral serology is relatively common in some regions where ARF is also common. False positive arboviral IgMs are also quite common. Therefore, positive arboviral serology does not exclude ARF, but negative serology helps to exclude arboviral infection.

f. Numerators

Cases of ARF occurring in a defined period of time will form the numerator in the incidence calculation. It is important that each case satisfies the case definition AND comes from the denominator population. This can be a problem where, for example, surveillance is conducted in a hospital that provides tertiary level care. Such a hospital may also potentially admit ARF patients from other regions. Such patients should not be included unless they were resident in the denominator region for 30 days or more prior to the onset of ARF symptoms (excluding pure chorea, in which case they should have been resident in the region for at least 6 months prior to the onset of symptoms). Therefore, it is critical to determine if the residential address of people with ARF is also the same as the place they have been residing over the previous 1-6 months.

g. Denominators

The denominator (person-years at risk) is equally important, and usually more difficult to calculate in population-based surveillance. Because ARF is a relatively rare disease in most populations, it is preferable to conduct surveillance in a large denominator population in order to maximize the number of ARF cases ascertained (and thus to minimize the confidence intervals surrounding the point estimate of disease incidence). However, larger denominator populations may make it more

difficult to ascertain all cases, particularly if the population is drained by numerous hospitals, or if there is a substantial likelihood that cases occurring within the surveillance region may attend a hospital outside of the surveillance region. An alternative is to conduct surveillance in a smaller population over a longer period of time, thus increasing the person-years at risk.

The denominator population should be defined before surveillance begins. The considerations in choosing a population include:

- Likely incidence of ARF
- Representativeness of the wider population that results are to be extrapolated to
- Accuracy of total and age-subgroup population data
- Ease of case ascertainment (including number and accessibility of surveillance sites / hospitals, and likelihood that cases will attend these hospitals)
- Availability of trained staff to conduct surveillance
- Quality of record keeping in hospitals, or potential to improve this
- Availability and quality of tests to investigate potential ARF cases, including haematology, biochemistry, serology, bacteriology and echocardiography.

h. Active or passive surveillance

Passive surveillance (relying on existing systems of disease notification) is rarely adequate for ARF case ascertainment. Even in regions where ARF is notifiable by legislation, many cased do not get notified to public health authorities. Relying on hospital discharge diagnosis data is often unreliable, because cases can be misdiagnosed (particularly by clinicians inexperienced in ARF diagnosis, or who do not adhere to the Jones or WHO criteria), the clinical information needed to confirm the diagnosis is often not recorded in medical notes, and/or many patients are incompletely investigated or observed. Passive surveillance will result in a high proportion of probable compared to definite cases, as well as under-estimates of the overall incidence of ARF.

Therefore, ARF surveillance ideally should be active. There are different levels of active surveillance, ranging from systematic searches of hospital admission case logs and laboratory records, to systematic searches of primary care records and even periodic school surveys. In most cases, hospital-based surveillance is the most practical use of resources. This requires setting up a multi-level strategy for case ascertainment (see "Identification of potential cases" above) and measures to ensure that potential cases are identified early after presentation, so that investigations and data collection are complete.

i. Quality control

Study personnel other than the one(s) who completed the form should review case report forms. Review should occur as quickly as possible after the form is completed. The reviewer is to audit whether all required fields are completed, whether appropriate data recording techniques were used (single lines through corrections, legible entries, etc), and whether there are logical inconsistencies in the source data. A systematic plan for performance of this quality control should be decided upon prior to the beginning of the surveillance effort.

3. Core elements of case report forms

Below are elements that are highly recommended to be included in all case report forms (bold) and other suggested elements for possible inclusion (normal type).

- **Date and time that CRF is completed**
- **Unique participant ID number**
- **Clinical site at which child is seen**
- **Other identifiers such as name, initials, date of birth, address**
- **Age and gender**
- **Date of symptom onset**
- **Date of admission to hospital**
- **Date of discharge from hospital**
- **Past history of ARF (Definite, Possible, No)**
    - Date of last episode ARF
    - Manifestations of ARF at prior episodes
- **Underlying pre-existing RHD (Yes, No, Not known)**
    - Valves affected and severity of pre-existing RHD
- Is the patient on the ARF/RHD register (Y/N)
- Already on secondary prophylaxis? (Y/N)
- Date of last dose BPG or estimated % missed doses oral prophylaxis in last month
- Medication received prior to hospitalization:
    - Anti-inflammatory
        - Paracetamol/acetaminophen
        - Codeine
        - Naproxen
        - Other (specify)
    - Antibiotic
        - Benzathine penicillin G
        - Oral penicillin
        - Other (specify)

Diagnostic category

- **Definite Primary, Probable primary, definite recurrent, probable recurrent**

Major manifestations (Y/N)

- **Carditis**
    - Specify valve lesion (MR, AR, MS, AS, TR – tick all that apply or grade severity mild/mod/sev)
    - Echocardiogram performed
    - Cardiac failure present
- **Polyarthritis**
    - Specify joints (ankle, knee, hip, wrists, elbow, shoulder, other)

    - Migratory (Y/N)
- **Chorea**
- **Erythema marginatum**
- **Subcutaneous nodules**

Minor manifestations (Y/N)

- **Fever**
    - Specify peak temp (°C)
- **Polyarthralgia**
    - Specify joints (ankle, knee, hip, wrists, elbow, shoulder, other)
- **(Monoarthritis)**
    - Specify joint (ankle, knee, hip, wrists, elbow, shoulder, other)
- **Raised ESR**
    - Specify peak
- **Raised CRP**
    - Specify peak
- **Prolonged PR interval**
    - Specify

Evidence of preceding group A streptococcal infection

- **Throat swab for culture (GAS positive / GAS negative / not done)**
- **Throat swab for rapid antigen (GAS positive / GAS negative / not done)**
- **ASO titer (Date taken and titer, date and titer if repeated)**
- **Anti-DNase B titer (Date taken and titer, date and titer if repeated)**
- **Recent scarlet fever (Y/N – if yes, date of onset)**
- Has the patient had a recent sore throat (Y/N – if yes, date of onset)

Other investigations

- Blood culture (Y/N, Date, Result)
- Joint aspiration (Y/N, Date, Result)
- Chest X-ray (Y/N, Date, Result)
- Copper, caeruloplasmin (Y/N, Date, Result)
- ANA (Y/N, Date, Result)
- Drug screen (Y/N, Date, Result)
- Other serology (Specify, Date, Result)

Treatment and progress

- Antibiotics (Y/N)
    - Benzathine penicillin / oral penicillin / Other
- NSAIDS (Y/N)
    - Aspirin / naproxen / other
- Corticosteroids (Y/N)
- Anti- cardiac failure medications (Y/N)

- Chorea medications (Y/N)
    - Carbamazepine / Valproic Acid / Haloperidol / Other
- Other medications (Specify)
- Acute cardiac intervention (Y/N)
    - Balloon valvuloplasty / Valve repair / Valve replacement
        - Give details of surgery – valve, date, type of prosthesis
- Formal education for patient and family started in hospital (Y/N)
- Notified to central ARF/RHD register (Y/N)
- Notified to local ARF/RHD register and/or primary care provider (Y/N)
- Given dose of secondary prophylaxis in hospital (Y/N, date)

4. Standardization of laboratory and echocardiographic testing

Standard guidelines, or standard operating procedures, should be adhered to where possible. Some of these have been developed, and others require development.

a. Throat swab collection and transport: See Standardized of epidemiologic protocols for surveillance of acute diseases caused by *Streptococcus pyogenes*: pharyngitis, impetigo and invasive diseases.
b. Rapid antigen testing: Needed
c. Culturing of swabs, isolation and grouping of group A streptococci and storage of swabs and isolates: See Standardized of epidemiologic protocols for surveillance of acute diseases caused by *Streptococcus pyogenes*: pharyngitis, impetigo and invasive diseases.
d. See Measurement of anti-streptolysin O antibodies (Needed)
e. Measurement of anti-DNase B antibodies (Needed)
f. Echocardiography in the diagnosis of rheumatic valvular disease (Needed)

Rheumatic heart disease

1. Case definition

Rheumatic heart disease (RHD) cases will be categorized as definite, probable or possible. If an echocardiogram has been performed that is inconsistent with the clinical findings, the echocardiographic findings will take precedence (e.g. a person with clinical findings consistent with significant mitral regurgitation, but with an echocardiogram that is normal or only showing trivial mitral regurgitation, will be categorized as not having RHD).

The following definitions should be applied only for people who do not have evidence of acute rheumatic fever. People with symptoms suggestive of ARF (see ARF surveillance protocol) should be managed accordingly and re-evaluated for the presence of rheumatic heart disease once active rheumatic inflammation has subsided.

Definitions of significant valve lesions on echocardiography:

Significant mitral stenosis is evidence of flow acceleration across the mitral valve with a mean pressure gradient greater than 4mmHg.

Significant mitral regurgitation is a mitral regurgitant jet at least 2 cm from the coaptation point of the valve leaflets, seen in two planes, high velocity (mosaic pattern) and persisting throughout systole.

Significant aortic regurgitation is an aortic regurgitant jet at least 1 cm from the coaptation point of the valve leaflets, of high velocity (mosaic pattern) and seen in two planes.

A. Definite rheumatic heart disease (any of):

a. Significant mitral stenosis on echocardiography **or** clinical findings of mitral stenosis with or without other valvular lesions. Additional echocardiographic changes that may be present include thickening of the mitral valve leaflets, "elbow" or "dog-leg" deformity of the anterior mitral valve leaflet, fixed or markedly restricted motion of the posterior mitral leaflet, calcification and commissural thickening.

b. The presence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation **and** echocardiographic evidence of rheumatic valvular damage, defined as **any of**:
    i. Significant mitral regurgitation **plus** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet. Additional changes that may be present include multiple regurgitant jets and/or a posterolaterally-directed jet.

    ii. Significant aortic regurgitation **plus** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet **without** another evident etiology for aortic insufficiency, such as bicuspid valve or annuloaortic ectasia.

Additional changes that may be present include aortic stenosis, but aortic stenosis without associated mitral valve disease will not be accepted as evidence of definite rheumatic valvular disease.

c. The presence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation **and** a past history of definite or probable ARF **and** echocardiogram not performed.

B. Probable rheumatic heart disease (either of):

a. The presence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation **and** person comes from a population with known or suspected high rates of ARF and/or RHD **and** no past history of definite or probable ARF **and any** of the following findings are present on echocardiography:

   i. Thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet **without** significant mitral stenosis, mitral regurgitation or aortic regurgitation.

   ii. Significant mitral regurgitation **without** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet

   iii. Significant aortic regurgitation **without** thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet.

b. The presence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation **and** person comes from a population with known or suspected high rates of ARF and/or RHD **and** no past history of definite or probable ARF **and** echocardiogram not performed

C. Possible Rheumatic Heart Disease:

a. In the absence of a heart murmur consistent with any combination of mitral regurgitation or aortic regurgitation, **and** person comes from a population with known or suspected high rates of ARF and/or RHD **any of** the following echocardiographic changes:

   i. Thickened mitral valve leaflets and/or elbow or dog leg deformity of the anterior mitral valve leaflet.

   ii. Significant mitral regurgitation

   iii. Significant aortic regurgitation

Implications for secondary prophylaxis and follow-up

Investigators should ensure that they have a pre-determined policy for administration of secondary prophylaxis and clinical follow-up of individuals given a diagnosis of Definite, Probable or Possible RHD. All people with Definite RHD should receive secondary prophylaxis according to local guidelines – these may be as recommended by the WHO Expert Writing Group, or local adaptations. In settings with high rates of ARF and RHD, consideration should also be given to managing all people with Probable RHD according to the same protocol. The management of people with Possible RHD may vary according to local considerations. In some settings, individuals with Possible RHD will be managed in the same way as those with Definite or Probable RHD. In other

settings, it may be appropriate to offer people with Possible RHD secondary prophylaxis for a defined period (e.g. 6-12 months) before re-assessing clinically and with echocardiography, with subsequent management being guided by the status at re-assessment.

In addition, it is essential that investigators consider in advance the availability of secondary prophylaxis in the settings in which case ascertainment will occur. This is particularly relevant if screening is to be undertaken. It would not be appropriate to undertake screening for RHD if there is no capacity, or no prospects for development of a capacity, to deliver secondary prophylaxis to individuals diagnosed with RHD during screening.

2. Aspects of surveillance and expression of disease occurrence

The primary goal of surveillance for RHD is to determine the prevalence of disease, usually stated as cases per 1,000 people at a particular time. RHD prevalence varies with age. The age group and the date to which the prevalence estimate refers should be clearly defined.

A secondary goal of surveillance may be to determine the prevalence of people with a history of ARF or RHD, who do not have RHD currently. This is discussed below.

a. Age groups:

Although the peak incidence of ARF is in children aged 5 to 14 years, the prevalence of RHD increases in older age groups, because RHD is the result of cumulative heart damage from earlier episodes of ARF. In most populations, the prevalence of RHD peaks in adults aged 20-40 years. However, the measurements most commonly used are prevalence in all ages, and in children aged 5-14 years. Sometimes school-based surveillance (see below) covers a narrower age range (e.g. primary school surveillance may only include children aged 5 to10 or 12 years); in this case the actual age range covered should be clearly stated. Investigators may also choose to report the prevalence in other age sub-groups, preferably divided into 10 year blocks (e.g. 15-24, 25-34, etc.).

b. Identification of potential cases:

There are two mechanisms for conducting RHD surveillance: passive and active. Passive surveillance can usually include a large denominator population, and is useful for determining clinically significant disease burden and planning and monitoring health service delivery and health policy. Because it is highly dependent on case ascertainment by existing health services, passive surveillance is not reliable for evaluating the efficacy of specific interventions such as vaccines. Active surveillance is targeted at smaller population groups and is more accurate. It can be used to augment passive surveillance in the measurement of disease burden, or for gaining a precise measurement of RHD prevalence in a research setting (e.g. for a clinical trial of an intervention such as a vaccine).

i. Passive surveillance: This relies on identifying cases that have been diagnosed with RHD by existing health services. The completeness of case ascertainment depends on the extent of case identification by the investigating team, and the presence of existing case registers. Potential sources of information about RHD cases, in order from the least to most complex and labour-intensive, include:

- Lists of people admitted to hospital with a primary or secondary diagnosis of RHD or ARF.

- Lists of people undergoing, or being considered for, surgery or other interventions for RHD.

- Lists of people reviewed by specialist cardiologists, physicians or paediatricians with a diagnosis of RHD or ARF.

- Lists of people receiving secondary prophylaxis.

- Lists of people having echocardiograms, in which the diagnosis is RHD.

- Reviewing a wider range of presentations to hospital and/or primary care services with diagnoses that could potentially be ARF or RHD (e.g. those with cardiac failure, fever and arthritis, abnormal movements, etc).

All of these measures can be applied retrospectively (i.e. gaining information from patients seen by health services previously) or prospectively (i.e. setting up mechanisms for identifying new patients as they present). The investigators should ensure that the maximum amount of information that is available is collated to determine whether the diagnosis is definite RHD, probable RHD, or not RHD. If possible, the investigators may need to organize clinical or echocardiographic review to confirm the status of particular cases. It is also important that the last date of review and the status at that date are recorded. The investigators should maintain a list of people who do not satisfy the diagnostic criteria, but in whom they are suspicious of a diagnosis of RHD, so that these people can be reviewed and reclassified as needed.

ii. Active surveillance: This refers to the conduct of cross-sectional surveys to identify previously-undiagnosed cases of RHD. Because RHD may remain asymptomatic for many years, and in some populations many affected people do not report a prior diagnosis of ARF or RHD, active surveillance is the most complete form of case ascertainment for RHD. The major issues in conducting surveys are selection of the sample, and methodology of diagnosis.

Selection of sample: In most cases, surveillance is conducted in school-age children for convenience, even though RHD prevalence is higher in adults. Adult surveillance may be possible in small populations – e.g. individual villages – but the history of screening in adult populations suggests that even the most comprehensive and expensive attempts to reach the majority of adults are unsuccessful. The remaining comments in this section apply to screening of school-aged children.

Surveillance is usually conducted at schools, so requires the cooperation of educational authorities. In selecting the sample, the following considerations should be taken into account:

a. Sample size: A power calculation should be performed, guided by the desired precision around the expected point estimate of prevalence. For example, a sample size of 2,000 children will provide a 95% CI ranging from 2.3% to 3.8% around a point RHD prevalence estimate of 3% (30 per 1,000), or a 95% CI ranging from 0.11% to 0.65% around a point estimate of 0.3% (3 per 1,000). In general, smaller samples (e.g. <1,000 children) are discouraged because of the reduced power they provide. Larger samples provide narrower confidence intervals and also serve to identify more children with previously undiagnosed RHD, to whom appropriate treatment and secondary prophylaxis can be offered.

b. Representativeness of sample. The children surveyed should, as much as possible, be representative of the wider population to whom the results are to be extrapolated. Considerations here include:

- Private compared to public schools. Socioeconomic status is a determinant of RHD prevalence, so in some areas children attending public schools may be expected to have higher RHD prevalence rates than those attending private schools.

- School attendance rates. In a population with high levels of school absenteeism, surveying school attendees will lead to selection bias. This bias will usually result in an under-estimate of RHD prevalence, as factors associated with school non-attendance (often related to poverty and/or ill health) may also be related to risk of RHD. The bias should be acknowledged (and school attendance rates cited) and if possible attempts should be made to survey school non-attenders as well. This is more difficult and costly.

- Location of schools: RHD prevalence can have geographic variation (for example, in most countries, the highest rates are found in urban slum areas, followed in descending order by rural areas and urban non-slum areas). The sample selection should ideally include representative schools from each of these areas.

- Selection of children within schools: Because of the potential for a clustering effect (i.e. that the risk of RHD in children attending a particular school may be different than for children attending another school) a survey should ideally cover many schools. This increases cost, but also increases external validity. The options include surveying all children in different schools, or surveying a subset of children in each school (and hence potentially increasing further the number of schools included). If the latter is chosen, an appropriate method of selection within schools should be chosen – i.e. a random sample of children or of classes (this latter method leaves open the possibility of a clustering effect by class).

Screening procedure. Most screening studies have undertaken auscultation, sometimes followed by echocardiography of children with murmurs (either all children with murmurs, or only children with murmurs deemed to be clinically significant). Auscultation is more logistically feasible, and echocardiography is more accurate. Echocardiography is particularly useful in school-age children, because the majority of children with RHD can be expected to have mild valve lesions that may be difficult to differentiate clinically from innocent murmurs. This is because children usually have not had multiple ARF recurrences, whereas adults with RHD have had a longer opportunity to develop recurrent ARF (and hence worsening RHD) and for the development of mitral or aortic stenosis.

Figure 1 outlines the potential approaches to screening. If the aim of auscultation is to detect any murmur, this can be performed by someone with relatively low-level training (e.g. a nurse, medical assistant or medical student). If the aim is to differentiate innocent from clinically significant murmurs, higher level training is required, and it has been well documented that even highly trained specialists vary in their ability to detect pathology compared to the gold standard of echocardiography. Moreover, in populations with high prevalence rates of RHD, highly trained clinical staff are often not available for surveillance activities. In a recent study in Tonga, specialist paediatricians asked to identify clinically significant murmurs were poorly sensitive and also not highly specific in detecting echocardiographically-confirmed RHD, whereas a medical student trained

to detect any murmur was highly sensitive but poorly specific (data submitted for publication and presented at Lancefield 2005, J Carapetis et al).

Therefore, until further data are available, the investigator should tailor their screening procedure to the available resources (skilled staff, funding, echocardiography) and the requirements for precision. If the primary aim is to provide disease burden data for public health priority setting or to identify RHD cases as part of health service delivery, then highly sensitive measures may not be needed. In this case, it may appropriate to use trained auscultators to detect clinically significant lesions, accepting that this will lead to mis-diagnosis of a substantial number of cases. If this can be augmented by echocardiographic confirmation of those with significant murmurs, then over-diagnosis will be avoided. The level of under-diagnosis will be determined by factors including the skill of the auscultator, which should be clearly stated. To reduce the workload for highly trained auscultators, a first stage auscultation by a nurse, medical assistant or medical student can be used to identify children with murmurs, who can then proceed to second stage auscultation by a specialist auscultator.

To avoid under-diagnosis, a single stage auscultation can be employed, in which the aim is simply to detect children with any murmur, significant or not. Children with murmurs all then undergo echocardiography. This has the advantage of high sensitivity and specificity, but also increases substantially the need for echocardiography (which should be balanced against the fact that a specialist auscultator is not needed) and may result in pickup of some children with so-called subclinical carditis.

If the primary aim is to provide data in the setting of an intervention (e.g. vaccine) study, then before and after methodology should be identical.

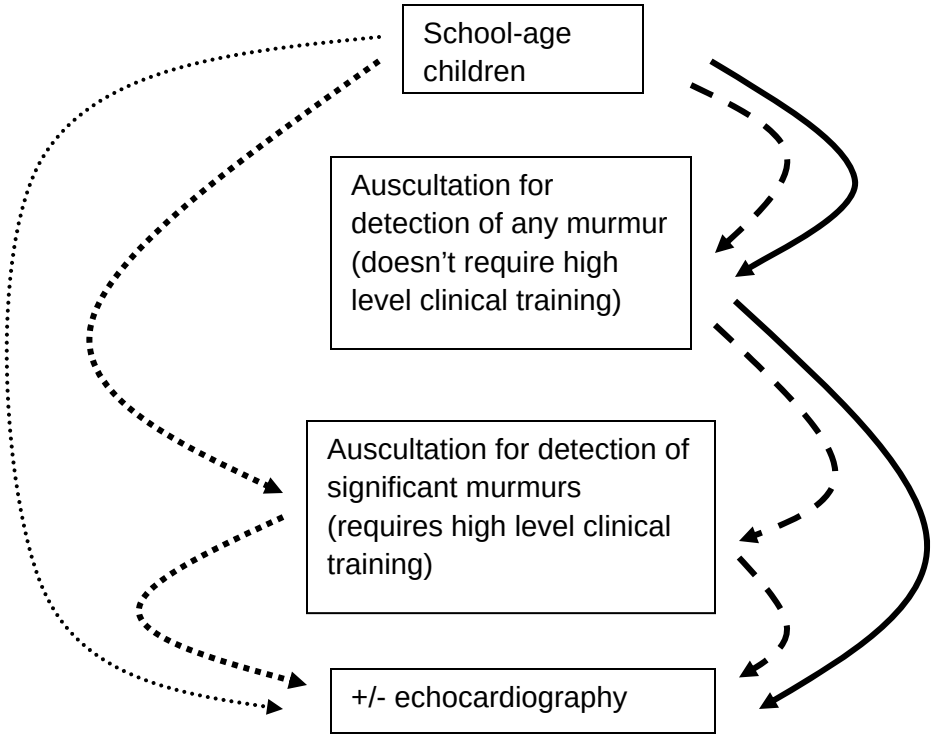

Figure 1. Options for screening for rheumatic heart disease in school-aged children.
Solid line: Single-stage auscultation followed by echocardiography of any child with a murmur. This is the ideal for sensitivity and specificity, but is highly dependent on availability of echocardiography. Dashed line: Two-stage auscultation, with or without echocardiography of children with significant murmurs. May be more practical, but second stage of auscultation may result in loss of sensitivity. Dotted line: Single-stage auscultation with or without echocardiography of any child with a significant murmur. Highly dependent on availability of specialized auscultators, and may result in reduced sensitivity. Fine dotted line: Echocardiographic screening of all children without auscultation. Will detect all clinical and subclinical disease. Not recommended at present.

Echocardiography: Modern portable echocardiography devices allow for the accurate diagnosis of RHD at field sites. A brief examination concentrating on the mitral and aortic valves can give sufficient information to diagnose and grade severity of RHD lesions and will take only 5 or 10 minutes per person. Such an examination would include parasternal long axis and apical four chamber views noting valve morphology on cross-sectional two-dimensional imaging and the degree and extent of mitral and aortic regurgitation using colour flow Doppler. Transvalvular flow is assessed by measuring the peak velocity with continuous wave Doppler. Views need not be taken of the tricuspid and pulmonary valves unless there is severe disease of mitral or aortic valves. Such views may pick up other major pathology (e.g. more severe septal defects) but will not give comprehensive structural detail of other aspects of cardiac anatomy.

c. Numerators

Cases of RHD presumed to be present at one time in the population will form the numerator for the prevalence calculation. It is sometimes difficult to be sure about the current status of cases detected by passive surveillance; e.g. should a case last seen two years previously, who at the time had mild RHD, be considered a prevalent case today? Therefore, every effort should be made to obtain up-to-date clinical and/or echocardiographic information about all potential RHD cases. Where this is not possible, it is recommended that cases may be recorded as having RHD if they had RHD of mild or moderate severity at their last review, this review occurred within the previous 3 years and the person is presumed to be still alive and living in the surveillance region. People with severe RHD (including those who have undergone valve surgery or valvuloplasty) may be considered prevalent cases if last seen within the previous 5 years and presumed to be still living in the surveillance region.

It is important that each case satisfies the case definition AND comes from the denominator population. This can be a problem where, for example, cases are ascertained through a hospital that provides tertiary level care. Such a hospital may also potentially admit RHD patients from other regions. Therefore, it is important to instigate measures to check current residential addresses of prevalent cases.

d. Denominators

The denominator (persons at risk) is equally important, and usually more difficult to calculate in population-based surveillance. Because RHD is a relatively rare disease in most populations, it is preferable to conduct passive surveillance in a large denominator population in order to maximize the number of RHD cases ascertained (and thus to minimize the confidence intervals surrounding the point estimate of disease prevalence). However, larger denominator populations may make it more difficult to ascertain all cases, particularly if the population is drained by numerous hospitals, or if there is a substantial likelihood that cases occurring within the surveillance region may attend health services outside of the surveillance region.

The denominator population should preferably be defined before surveillance begins. The considerations in choosing a population include:

- Likely prevalence of RHD.
- Representativeness of the wider population that results are to be extrapolated to
- Accuracy of total and age-subgroup population data
- Ease of case ascertainment (including number and accessibility of surveillance sites / hospitals, availability of patient lists from other sources, presence of existing case registers)
- Availability of trained staff to conduct surveillance
- Quality of record keeping in hospitals, or potential to improve this
- Availability and quality of echocardiography.

e. Privacy concerns

Maintenance of disease registers that contain identifying details of individuals may be considered sensitive in some regions. There may be local legislation or other ethical standards that mandate particular approval processes before data can be collected. This may range from gaining Ministry of Health approval, to Institutional Review Board approval, to consent of opinion leaders in the

community, to written informed consent of all registered people. The local requirements should be considered at an early stage of planning by investigators.

f. Quality control

Study personnel other than the one(s) who completed the form should review case report forms. Review should occur as quickly as possible after the form is completed. The reviewer is to audit whether all required fields are completed, whether appropriate data recording techniques were used (single lines through corrections, legible entries, etc), and whether there are logical inconsistencies in the source data. A systematic plan for performance of this quality control should be decided upon prior to the beginning of the surveillance effort.

g. A history of acute rheumatic fever or rheumatic heart disease

The prevalence of rheumatic heart disease in a population does not give a complete representation of the impact of ARF and RHD in a community at a single point in time, because there will be others in the community who have previously had ARF or RHD, but who currently do not have persistent valvular damage. These people represent the burden of ARF in previous years, and many require secondary prophylaxis for years to come. The prevalence of individuals with a past history of ARF or RHD who currently receive, or should be receiving, secondary prophylaxis should be included in any estimate of the disease burden due to ARF and RHD in a population. Those who have had ARF or RHD but no longer have RHD and no longer receive, or should be receiving, secondary prophylaxis are of less interest as they place minimal demands on health services as a direct result of their ARF/RHD history.

Identification of people without RHD, but receiving secondary prophylaxis, is usually possible through passive surveillance where secondary prophylaxis registers are maintained. Where secondary prophylaxis registers are not maintained, or where the aim is to identify people without RHD who should be receiving secondary prophylaxis but who do not appear on secondary prophylaxis registers, case identification is more difficult. This requires either a careful exercise of retrospective identification of ARF and RHD cases with active follow-up to determine current status. This is often considered too difficult and labour intensive, and instead estimates may be made based on the incidence of ARF and the proportion likely not to develop subsequent RHD but to require ongoing secondary prophylaxis. For example, it is commonly estimated that 40% of ARF cases will not develop RHD, and that the average duration of secondary prophylaxis after the diagnosis of ARF is 10 years.

3. Core elements of case report forms

Below are elements that are highly recommended to be included in all case report forms (bold) and other suggested elements for possible inclusion (normal type).

- **Date and time that CRF is completed**
- **Unique participant ID number**

- **Clinical site at which participant is seen (for active surveillance)**
- **Other identifiers such as name, initials, date of birth, address**
- **Age and gender**
- Past history of ARF (Definite, Possible, No)
    - Date of last episode ARF
- Date of first diagnosis of RHD
- History of RHD valve surgery or valvuloplasty (Y/N)
    - Type of intervention, date and place
- Complications of RHD and date
    - Stroke
    - Infective endocarditis
    - Atrial fibrillation
    - Other (Specify)
- **Date of most recent clinical review**
    - **Review by (specialist, primary care doctor, nurse, health worker)**
    - **Echocardiogram performed (Y/N)**
    - **Status at most recent review**
        - **NYHA Grading**
        - **Overall status of RHD**
            - **Definite RHD (Mild/Mod/Sev)**
            - **Probable RHD (Subclinical/Mild/Mod/Sev)**
        - Status of valve lesions (Circle all that apply)
            - MR – Mild/Mod/Sev
            - AR – Mild/Mod/Sev
            - MS – Mild/Mod/Sev
            - AS – Mild/Mod/Sev
            - Other (specify)
    - Medications
        - Secondary prophylaxis
            - Benzathine penicillin G – 2/3/4 weekly
            - Oral penicillin V
            - Erythromycin
            - Other
        - Warfarin
        - Anti-failure medications (specify)
    - **If no echocardiogram at most recent review, date of last echo**
        - **Echo findings**

For active surveillance (screening):

- **Murmur present (Y/N)**
- **Clinical diagnosis (Innocent, MR, MS, AR, AS, VSD, Other – For all of the pathological diagnoses, circle all that apply and give grading of mild/mod/sev)**
    - Signs of heart failure (Y/N)

- **Echocardiographic diagnosis (Innocent, MR, MS, AR, AS, VSD, Other – For all of the pathological diagnoses, circle all that apply and give grading of mild/mod/sev)**
    - **Details of echocardiographic findings**

4. Standardization of echocardiographic testing

There is a need for a protocol to ensure consistency of echocardiogram reading. Efforts are presently underway to devise this.

Acute post-streptococcal glomerulonephritis

1. Case definition

Acute post-streptococcal glomerulonephritis (APSGN) can be clinical (with symptoms and/or signs) or subclinical (without symptoms or signs other than abnormal urinary sediment). The ratio of subclinical:clinical cases in outbreaks varies between studies, but may be as high as five or ten to one. Subclinical cases can only be detected by screening people who are contacts of clinical cases. In most cases, APSGN surveillance will focus on the ascertainment of clinical cases.

Confirmation of APSGN requires not only the presence of certain clinical features, but also positive results from laboratory tests. Specifically, laboratory tests are needed to confirm an antecedent group A streptococcal infection and to identify hypocomplementaemia. Although some case definitions have not made low C3 and/or C4 levels obligatory for the diagnosis, the available evidence suggests that a low C3 in particular is the best test for differentiating post-streptococcal from other forms of glomerulonephritis.

Some or all of these tests may not be available at surveillance sites, or may not be performed in some possible cases. Therefore, APSGN cases will be considered definite if laboratory confirmation is available, or probable if laboratory confirmation is not available.

There are four possible categories of APSGN:

- Definite clinical APSGN
- Probable clinical APSGN
- Definite subclinical APSGN
- Probable subclinical APSGN

a. Definite Clinical APSGN*

The presence of TWO OR MORE of the following:

1. Macroscopic or microscopic hematuria (>10 red blood cells/mm^3 on urine microscopy or $\geq$2+ on urine dipstick)
2. Oedema (any of definite facial puffiness, pitting peripheral oedema, ascites, or other clear evidence of oedema)
3. Hypertension (diastolic blood pressure >90mmHg in children 13 years and older or >80mmHg in children <13 years)

AND

Reduced serum C3 level (tested within four weeks of symptom onset)**

AND

Evidence of antecedent streptococcal infection*** (Elevated or rising ASO or anti-DNase B titers OR isolation of GAS from throat or skin sore culture OR positive rapid antigen test from throat swab)

* This is the case definition of the Ministry of Health of the Northern Territory, Australia. (See *The Northern Territory Disease Control Bulletin* 2001;**8:**1-40.)

** See below under complement assays.

*** See below under evidence of antecedent streptococcal infection

b. Probable Clinical APSGN

The presence of two or more of the following:

1. Macroscopic or microscopic hematuria (>10 red blood cells/mm^3 on urine microscopy or ≥2+ on urine dipstick)
2. Oedema (any of definite facial puffiness, pitting peripheral oedema, ascites, or other clear evidence of oedema)
3. Hypertension (diastolic blood pressure >90mmHg in children 13 years and older or >80mmHg in children <13 years)

AND ANY OF

1. Both C3 level and tests for antecedent streptococcal infection not performed.
2. Low C3 level or normal C3 level tested >4 weeks after symptom onset, but tests to confirm antecedent streptococcal infection not performed
3. Evidence of antecedent streptococcal infection but C3 test not performed.

c. Definite subclinical APSGN

The presence of microscopic hematuria (>10 red blood cells/mm^3 on urine microscopy or ≥2+ on urine dipstick) in a person who is a contact (i.e. has close personal contact or lives in the same small community or village) of a case of definite or probable clinical APSGN

AND

Reduced serum C3 level

AND

Evidence of antecedent streptococcal infection (Elevated or rising ASO or anti-DNase B titers OR isolation of GAS from throat or skin sore culture OR positive rapid antigen test from throat swab)

d. Probable subclinical APSGN

The presence of microscopic hematuria (>10 red blood cells/mm^3 on urine microscopy or ≥2+ on urine dipstick) in a person who is a contact (i.e. has close personal contact or lives in the same small community or village) of a case of definite or probable clinical APSGN

AND

Low C3 level but tests to confirm antecedent streptococcal infection not performed

Note that, because abnormal urinary sediment can be common in some communities with high rates of APSGN, and in these communities background anti-streptococcal antibody titers are often elevated, all subclinical cases require evidence of low C3. Elevated anti-streptococcal antibody titers in the absence of a C3 level is not sufficient to qualify as a probable subclinical case.

Notes about case definition

i. Elevated or rising streptococcal antibody titers.

It is recommended that acute serum be collected at the onset of illness, and that the antibody titer be compared to a convalescent serum collected 2-4 weeks later, to detect a rise in titer.

When paired acute and convalescent titers are not available, an upper limit of normal (ULN) value may be used on a single serum. It is recommended that age-stratified ULN values for serum streptococcal antibody titers be determined in a subset of individuals without a recent streptococcal infection in each population if possible. In many populations, this may not be possible for reasons of logistics, cost, or simply because streptococcal infections are so highly prevalent that it is difficult to identify any children without recent streptococcal infections. In these situations, it is recommended that the ULN levels from three recent studies be used (Table 1).

Table 1. Recommended upper limits of normal for anti-streptolysin O and anti-DNase B titers, in the absence of appropriate local population data.

Age group (yrs)	Upper limit of normal	
	ASO titer	Anti-DNase B titer
2-4	160	240
5-9	240	320-640
10-12	320	480-640
>12	400	200

From: Kaplan EL et al, Pediatrics 1998; 101: 86-8; Gray GC et al. J Clin Epidemiol 1993; 46: 1181-5; and Karmarkar MG et al, Indian J Med Res. 2004;119 Suppl:26-8.

ii. Complement assays

Although a proportion of cases with APSGN has been reported to have normal C3 levels (see for example J Pediatr. 1974;84:29-38), most series that clearly document the post-streptococcal aetiology of nephritis have found transient hypocomplementemia to be present in all, or almost all, cases (see for example Pediatr Int. 2001;43:364-7). It should be noted that complement levels usually remain reduced for the first four weeks, but normalize within 8 weeks in 97% of patients and within 12 weeks in 100% (Pediatr Int. 2001;43:364-7). Therefore, a normal C3 that is tested >4 weeks after symptom onset cannot be used to exclude APSGN. Because there are other causes of low C3 levels in nephritis (e.g. in SLE), all cases should have normalization of their C3 level demonstrated 8-12 weeks after symptom onset.

iii. Differential diagnosis

Most clinical cases will present with a combination of clinical features consistent with nephritic syndrome (macroscopic hematuria, proteinuria, hypertension and oliguria). In a population with high incidence of APSGN, this clinical presentation together with evidence of antecedent streptococcal infection and low serum C3 (and/or C4) level is sufficient to make the diagnosis. Occasionally, other causes of nephritis (e.g. systemic lupus erythematosus) may cause a similar

presentation and low serum complement levels. In APSGN, the C3 should return to normal within 6 weeks. Therefore, C3 should always be repeated 6 weeks or more after presentation – if it remains depressed, alternative diagnoses (including SLE) should be considered.

The differential diagnosis of patients presenting with nephritic syndrome includes other post-infectious glomerulonephritis, IgA or IgM nephropathy, SLE, infective endocarditis, Henoch-Schonlein disease, anti-GBM disease, and Wegener's vasculitis. Some of these can be confirmed without a renal biopsy (e.g. infective endocarditis may be confirmed with cardiac examination, echocardiography and blood cultures, and SLE may be confirmed with autoimmune tests such as the anti-nuclear antibody), but most require renal biopsy and involvement of a specialist such as a nephrologists or rheumatologist.

Other causes of oedema (e.g. hypoproteinaemia, cardiac failure) can usually be excluded early in the clinical course, so it is rare for these cases to be confused with APSGN after an initial period of observation and some baseline investigations have been performed.

Therefore, surveillance of APSGN should ideally include a mechanism to double-check one to two months later that the diagnosis has not changed from APSGN to another cause of glomerulonephritis.

2. Aspects of surveillance and expression of disease occurrence

The goal of surveillance for APSGN is to determine the age-specific incidence of disease, usually stated as cases per 100,000 person-years. Therefore, the age group and duration of surveillance should be clearly defined.

a. Age:

The peak incidence of APSGN is in children aged <15 years. Therefore, APSGN surveillance should always include this age group, and data should always be produced separately for this age group. Investigators may also choose to include other age groups. For example, APSGN occurs from time to time in older adolescents and adults.

b. Duration of surveillance:

APSGN incidence is seasonal in many places, so surveillance should ideally take place over at least 12 months and in multiples of 12 months.

c. Site of ascertainment:

The more severe cases of clinical APSGN will present to hospital, so hospital-based surveillance is mandatory. Investigators should ensure that all hospitals or other clinical establishments (e.g. smaller clinics with inpatient facilities) in the drainage area that could reasonably be expected to manage APSGN patients are included. However, milder APSGN cases may be managed by primary care services or on an outpatient basis, although this would not be acceptable in most prospective studies. Investigators may choose to expand surveillance to include these settings. This approach increases the number of sites of surveillance, the cost, and the complexity; in particular, information (especially

clinical data recording and performance of tests) is often incomplete in primary care or outpatient settings. The sites of case ascertainment should be clearly stated, and the incidence of cases presenting to hospital should always be reported separately.

Detection of subclinical APSGN requires testing of asymptomatic contacts of people with APSGN. This is usually only done either for research purposes, or in response to a community outbreak of APSGN, to determine the size of the outbreak and/or to identify people for targeted interventions (e.g. antibiotics). However, most public health authorities choose instead to use outbreak definitions based on the number of clinical cases of APSGN in a defined population (e.g. two cases in a week or three cases in a month) and then to undertake interventions without screening (e.g. in the event of an outbreak of APSGN in an Aboriginal community in the Northern Territory of Australia, all family members of APSGN patients, and all children with skin sores, receive a single dose of benzathine penicillin G). It is not currently known if subclinical APSGN has any longer term implications for affected individuals, so screening for asymptomatic cases will remain, in most instances, a research tool.

d. Identification of potential cases:

It is suggested that multiple levels of case ascertainment be established, including routine review of all admissions with an over-inclusive list of admission diagnoses (as mentioned above), regular liaison with hospital medical staff in paediatrics and intensive care, and routine review of urine microscopy, serum complement and streptococcal serology results. Ideally, confirmation should be sought approximately two months after admission that cases initially thought to be APSGN have not been reclassified to alternative diagnoses.

e. Investigation of potential cases:

Possible APSGN cases need to have clear documentation of how they satisfy the diagnostic criteria. This usually means that the following investigations are needed on all cases (if available):

- Throat swab for culture (and/or rapid antigen test)
- Skin sore swab (if sores present) for culture
- Urine microscopy
- Anti-streptolysin O and anti-DNase B titers
- Serum complement level (C3 +/- C4)

A number of other investigations may be performed (e.g. urea, creatinine, electrolytes, antinuclear antibody, renal biopsy, quantitation of proteinura) to determine the severity of disease and to exclude other diagnoses, but the above are the core investigations that should be performed on everyone.

f. Numerators

Cases of APSGN occurring in a defined period of time will form the numerator in the incidence calculation. It is important that each case satisfies the case definition AND comes from the denominator population. This can be a problem where, for example, surveillance is conducted in a hospital that provides tertiary level care. Such a hospital may also potentially admit APSGN patients from other regions. Such patients should not be included unless they were resident in the

denominator region for 30 days or more prior to the onset of APSGN symptoms. Therefore, it is critical to determine if the residential address of people with APSGN is also the same as the place they have been residing over the previous month.

g. Denominators

The denominator (person-years at risk) is equally important, and usually more difficult to calculate in population-based surveillance. Because APSGN is a relatively rare disease in most populations, it is preferable to conduct surveillance in a large denominator population in order to maximize the number of APSGN cases ascertained (and thus to minimize the confidence intervals surrounding the point estimate of disease incidence). However, larger denominator populations may make it more difficult to ascertain all cases, particularly if the population is drained by numerous hospitals, or if there is a substantial likelihood that cases occurring within the surveillance region may attend a hospital outside of the surveillance region. An alternative is to conduct surveillance in a smaller population over a longer period of time, thus increasing the person-years at risk.

The denominator population should be defined before surveillance begins. The considerations in choosing a population include:

- Likely incidence of APSGN
- Representativeness of the wider population that results are to be extrapolated to
- Accuracy of total and age-subgroup population data
- Ease of case ascertainment (including number and accessibility of surveillance sites / hospitals, and likelihood that cases will attend these hospitals)
- Availability of trained staff to conduct surveillance
- Quality of record keeping in hospitals, or potential to improve this
- Availability and quality of tests to investigate potential APSGN cases, including haematology, biochemistry, serology, bacteriology and, if necessary, renal biopsy.

h. Active or passive surveillance

Passive surveillance is rarely adequate for APSGN case ascertainment. Even in regions where APSGN is notifiable by legislation, many cased do not get notified to public health authorities. Relying on hospital discharge diagnosis data is often unreliable, because cases can be misdiagnosed (particularly by clinicians inexperienced in APSGN diagnosis, especially as there are not universally agreed diagnostic criteria), the clinical information needed to confirm the diagnosis is often not recorded in medical notes, and/or many patients are incompletely investigated or observed. Passive surveillance will result in a high proportion of probable compared to definite cases, as well as under-estimates of the overall incidence of APSGN.

Therefore, APSGN surveillance ideally should be active. This requires setting up a multi-level strategy for case ascertainment (see "Identification of potential cases" above) and measures to ensure that potential cases are identified early after presentation, so that investigations and data collection are complete.

i. Quality control

Study personnel other than the one(s) who completed the form should review case report forms. Review should occur as quickly as possible after the form is completed. The reviewer is to audit

whether all required fields are completed, whether appropriate data recording techniques were used (single lines through corrections, legible entries, etc), and whether there are logical inconsistencies in the source data. A systematic plan for performance of this quality control should be decided upon prior to the beginning of the surveillance effort.

3. Core elements of case report forms

Below are elements that are highly recommended to be included in all case report forms (bold) and other suggested elements for possible inclusion (normal type).

- **Date and time that CRF is completed**
- **Unique participant ID number**
- **Clinical site at which child is seen**
- **Other identifiers such as name, initials, date of birth, address**
- **Age and gender**
- **Date of admission to hospital**
- **Date of discharge from hospital**
- Past history of APSGN (Definite, Possible, No)
    - Date of last episode APSGN
- Known contact of APSGN case (Y/N)
    - Give details:
- Antibiotic received prior to hospitalization:
    - Benzathine penicillin G
    - Oral penicillin
    - Other (specify)

Diagnostic category

- **Definite clinical, Probable clinical, definite subclinical, probable subclinical**

Diagnosis of APSGN

- **Hypertension (Y/N)**
    - Highest blood pressure (Systolic/Diastolic) I__I__I / I__I__I
- **Oedema (Y/N)**
    - Specify: facial puffiness, pitting peripheral oedema, ascites, other clear evidence of oedema
- **Hematuria (Macroscopic / Microscopic / No)**
    - Urine red cell count
- **Low C3 (Y/N)**
    - Date taken
    - C3 level
- Low C4 (Y/N)
    - Date taken
    - C4 level

Evidence of preceding group A streptococcal infection

- **Throat swab for culture (GAS positive / Other BHS positive (specify) / BHS negative / not done)**
- **Throat swab for rapid antigen (GAS positive / GAS negative / not done)**
- **Skin sore swab for culture (GAS positive / Other BHS positive (specify) / BHS negative / not done)**
- **ASO titer (Date taken and titer, date and titer if repeated)**
- **Anti-DNase B titer (Date taken and titer, date and titer if repeated)**
- Has the patient had a recent sore throat (Y/N – if yes, date of onset)
- Has the patient had a recent skin sore (Y/N – if yes, date of onset)

Other clinical information

- Proteinuria ≥2+ on dipstick (Y/N)
- Anuria (no urine for 24 hrs) (Y/N)
- Renal failure (Y/N)
    - Highest blood urea (Date and level)
    - Highest blood creatinine (Date and level)
    - Dialysis (Y/N and date if Y)
- Intensive care admission (Y/N)
- Renal biopsy (Y/N)
    - If yes, date and result:
- Anti-nuclear antibody (Y/N)
    - If yes, date and result:
- **Follow-up confirmation of Dx**
    - **APSGN diagnosis remains unchanged (Y/N)**
        - **Date of last follow-up:**
    - **C3 level re-tested and normal (Y/N)**
        - **Date of most recent testing and level:**

4. Standardization of laboratory testing

Standard guidelines, or standard operating procedures, should be adhered to where possible. Some of these have been developed, and others require development.

a. Throat swab collection and transport: See Standardized of epidemiologic protocols for surveillance of acute diseases caused by *Streptococcus pyogenes*: pharyngitis, impetigo and invasive diseases.
b. Rapid antigen testing: Needed
c. Skin sore swab collection and transport: Needed
d. Culturing of swabs, isolation and grouping of group A streptococci and storage of swabs and isolates: See Standardized of epidemiologic protocols for surveillance of acute diseases caused by *Streptococcus pyogenes*: pharyngitis, impetigo and invasive diseases.

e. Measurement of anti-streptolysin O antibodies (Needed)
f. Measurement of anti-DNase B antibodies (Needed)
g. Measurement of C3 levels (Needed)

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